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Local biologicals and the politics of standardization: Making ethical pluripotent stem cells in the United Kingdom and Japan

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Abstract In 2003, the United Kingdom and Japan had adopted relatively similar approaches to human embryonic stem cells science. The decade since has witnessed significant divergence in their national policies as differing responses to ethical questions about research use of human embryos emerged. The United Kingdom pursued a vision of 'institutionally accredited stem cells' by reconfiguring the role of the Human Fertilisation and Embryology Authority and establishing the UK Stem Cell Bank. In contrast, Japan followed a vision of 'technically advanced stem cells' by developing induced pluripotent stem cells and supporting its research programs enthusiastically. Our research – drawing upon extensive fieldwork in both countries – demonstrates the socio-technical arrangements developed to instantiate these visions and articulates their divergence while at the same time revealing their connectedness. This relationship becomes progressively evident as the two visions face each other in the politics of standardization in global stem cell science. Drawing on Franklin's concept of local/global biological, we discuss the connectedness of the two local arrangements. In so doing, we explicate the future challenges for both countries as they need to demonstrate the significance of their visions in this global enterprise, while the success of one would likely undermine the significance of the other.

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Introduction

In 2003, the UK Royal Academy of Engineering sent a mission to Japan resulting in the report "The Japanese Approach to Tissue Engineering". The mission identified familiar ethical issues about using human embryonic stem (hES) cells for research purposes as a major obstacle, and

in it they state that "there is no doubt that Japan faces very similar barriers to the successful commercial introduction of tissue engineering products and processes to those experienced in the UK and elsewhere" (Royal Academy of Engineering (UK) (RAoE), 2003, p. 3). While we agree with this statement from a 2003 perspective, in this article we argue the two countries subsequently took quite different approaches to dealing with the embryo issue, each of them underpinned by a globally recognized socio-technical arrangement: in the United Kingdom, the Human Fertilisation and Embryology (HFE) Act amendments and establishment of the UK Stem Cell Bank, and in Japan, the development of induced pluripotent stem (iPS) cells and the subsequent policy shift. Both of these arrangements attracted the attentions of many other countries, and have been adopted in some, including the establishment of national stem cell banks in Spain and the promotion of iPS cell research in the United States (Stephens *et al*, 2011a, 2013; Hammond-Browning and Stephens, 2013). Our analysis, however, reveals not only that these socio-technical arrangements take different forms framed by their national context but also that they pose serious challenge to each other at an international level, where they have to prove their global significance, allowing their stem cells to travel beyond their locality.

In this article we elaborate on this challenge through an analysis of practical, scientific and regulatory responses observed in the two countries before and after the development of human iPS cells in 2007. We choose these two countries because they represent international leadership in their respective socio-technical arrangements. We use this notion of socio-technical arrangements to capture the assemblage of institutional, symbolic, material and imagined practices that constitute what Franklin (2005) terms the "local biologicals" pursued in each country. To Franklin, stem cells can be understood as a global/local biological:

> [Stem cell] production is a global biological enterprise, but it is also their "global," in the sense of totalizing, projected uses to which this term refers. […] Stem cell technology is a prime example of the ways in which the global may come into being as a biocultural condition, as a form of identity, and as a realm of imaginary futures. At the same time, stem cell technology is also … a local biological. […] Stem cell technologies […] demonstrate how biological properties are increasingly not only being "discovered," but are being created, in ways that reveal specific national and economic priorities, moral and civic values, and technoscientific institutional cultures.
>
> (Franklin, 2005, p. 61)

By seeing a local biological as an assemblage, our analysis premises on the view that the local priorities and values it reflects can be heterogeneous and contested within its original context, and are also influenced by other local biologicals created elsewhere due to the globalizing nature of stem cell science and the complex flows of actors, institutions and narratives as its consequence. Therefore, the aims of this article are first to make explicit the specific priorities and values in the two countries and then to reveal the practical challenges in negotiating their differences and instantiating them in both local and global contexts.

The analysis divides into three sections. The first details the history until 2007, focusing upon the divergent trajectories taken in Japan and the United Kingdom, and the second examines the initial responses to iPS cell technology in both countries. Together these two sections demonstrate how the two nations attempt to instantiate their visions of 'institutionally accredited stem cells' in the United Kingdom and 'technically advanced stem cells' in Japan.

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The third section then develops the work of Hauskeller and Weber (2011) and Eriksson and Webster (2008) to articulate how these two socio-technical arrangements pose challenges for each other as we reveal the politics of standardization in international stem cell science. We necessarily adopt a slightly different tone for narrating the history in the first two sections from the discussion in the third section. In the first two sections we draw together the analysis of narrative data from policy documents, observations and interviews to report meanings and practices as produced by actors in the field. In the final section the onus shifts toward articulating our own original contribution by applying existing theory from Science and Technology Studies to allow us, as analysts, to speculate on future practice.

To preview our argument in succinct form, by 2003 both Japan and the United Kingdom attempted to provide a regulatory foundation for hES cell research that was both mindful of ethical concerns over embryo use while permissive and facilitative of an emerging stem cell bioeconomy. While the United Kingdom experienced a level of success through adapting existing regulatory structures and establishing the UK Stem Cell Bank, internal rigidities within the Japanese system prevented all but small quantities of hES cell research occurring. The stagnated Japanese stem cell research portfolio was radically transformed with the emergence of iPS cells as Japan reconfigured its vision for stem cell research and rapidly adjusted its institutional and regulatory system. While many UK scientists also engaged with iPS cell research, the institutional vision at nation-state level, and the administrative forms it supported, remained largely focused upon hES cell research. In contrast, stem cell research in Japan exhibited rapid expansion in iPS cell research since 2007 while the stagnation of hES cell research remained persistent. In doing so, these locally specific biological arrangements are progressively posing challenges to each other as they attempt to globalize, meaning both to internationalize and to totalize, their socio-technical arrangements. One of the battlefields for this contestment is to be found in the seemingly benign realm of standardization. In practice, as we demonstrate, while both approaches to stem cell science diverted off into different directions, both Japanese and UK researchers and institutional actors must respond to the ethical and technical potentials of the other, as iPS and hES cells, and the standardization procedures pursued with both, are used as referencing points by which the other is judged and notions of 'naturalness' and 'efficacy' are contested. These challenges now demand each of the countries engage with the approach that the other pursued earlier: a technical characterization of hES cells for the United Kingdom and an institutional validation of iPS cells for Japan.

Methodology

This article builds on two separate projects and we draw upon empirical data collected in them both. The first, conducted by Mikami, was a 3-year comparative interview study of tissue engineering in the United Kingdom and Japan. Mikami conducted 72 interviews with UK and Japanese scientists, regulators and other individuals engaged in the field. The second, conducted by Stephens, is a 3-year ethnographic study of the UK Stem Cell Bank that conducted observations and 36 interviews with staff at the bank, its guidance committee, regulatory bodies and laboratories that deposit stem cell lines at the Bank. These intensive data collection periods in the mid-to-late 2000s have been supplemented with continued engagement with the field up to the present date. Interviews and documents in Japanese have

been translated into English and analyzed by the first author. The data were first analyzed individually by the two authors and narratives of stem cell science in each of the two countries were studied. Comparing these country-specific narratives then allowed us to identify (i) the key instances in which their socio-technical arrangements were being (re-)shaped, and (ii) exactly what form this (re-)shaping took. We subsequently returned to our data focusing on grand narratives in both countries to arrive at the argument presented here.

The detailed qualitative analysis conducted inevitably gave rise to nuanced and complicated accounts of practice in each nation. In writing we are mindful of balancing these situated and sometimes contradictory accounts with the broader analytical framework of grand narratives emerging in both local and global biologicals. It is for this reason that we embed a notion of 'heterodoxy within' on conceptualization of local biologicals. This concern also frames the form of our analysis as the level of analysis we pursue involves conveying and comparing the grand narratives in each country without denying their local contestment. Such contestment is highlighted only when it is critical for explicating the connectedness of the two local biologicals in this article.

In our analysis, we worked with detailed and lengthy interview extracts ensuring our analysis responds closely to the contingency and complexity of these accounts. In reporting the interview data, however, we decided to keep it succinct and precise, using only interview data that work as clear articulations of core themes found in the data. Our decision was (i) to retain our focus on grand narratives, as stated earlier, and also (ii) to retain an appropriate quantity of interview material for the size and scope of our report.

We recognize, of course, that the United Kingdom and Japan are not the only countries active in stem cell research, and are not the only countries engaged in pursuing local and global aspirations in regenerative medicine. However, they do provide a sharp point of comparison around which we can develop our analytical framework. We are aware of the inherent challenge in basing our account on a comparison of two nations both operating within an international context. This challenge can be especially significant when comparing one 'Western' and one 'non-Western' country, that is, the United Kingdom and Japan, respectively. Such accounts can risk constructing Japan as a 'victim' of some form of Western imperialist strategizing (see, for example, Lock, 2002 for discussion of this risk). We avoid doing this as much as possible by focusing on individual countries in the earlier stage of our analysis. At the same time, we deliberately leave any sense of Western imperialism, or the aspiration in Japan to challenge such imperialism, in this article where the actors in our study themselves used such narratives.

2001–2007: A Shared Vision Unevenly Pursued

The 2003 Royal Academy of Engineering report suggests that Japan and the United Kingdom faced a set of similar challenges. The two governments recognized tissue engineering, or regenerative medicine, as an important innovation, a basis of regaining economic strength, and a potential mechanism for addressing the health issues of their aging populations. Both governments recognized the ongoing political and ethical debates about appropriate hES cell use. During their 5-day visit to Japan, the members of the mission visited two ministries, five research groups and five private companies. While they were impressed by the scale of investment the Japanese

government had made, they also judged its target to be unreasonably high, particularly noting that its investment had built world-class facilities but had not attracted world-class researchers. They were also concerned about the low level of private investment in the field, and pointed to uncertainties about how the technology would be utilized in clinical contexts. Furthermore, the mission observed that Japanese researchers tended to focus on the basic biology of stem cells, such as cell development, as opposed to engineering aspects, such as developing therapeutic products.

In 2001, both the United Kingdom and Japan were in the early stages of developing a regulatory structure to support a vision of productive but ethical stem cell science. The UK government had officially approved the use of human embryos for research purposes under strict conditions in as early as the 1990s and formed its regulatory structure building upon them (Hauskeller, 2004). The 1990 HFE Act legalized research use of human embryos for a limited set of five specific purposes (Department of Health (UK) (DoH), 1990, Schedule 2: Paragraph 3(2)). The Act invokes a concept of "early embryos", meaning "embryos before the appearance of the primitive streak" as observed on day 14 of development, as originally suggested in the Warnock Report of 1984 (cf. Mulkay, 1997). This first Act was focused upon reproductive health, but the raised attention on embryo research inspired by Thompson's 1998 derivation of the first hES cell line provoked a 2001 amendment to extend the scope of legitimate research to include:

(1) increasing knowledge about the development of embryos;
(2) increasing knowledge about serious diseases; and
(3) enabling any such knowledge to be applied in developing treatments for serious disease.

(DoH, 2001, Paragraph 2(2))

It resulted in a UK regulatory system recognized as both (i) highly regulated in that all hES cell derivation had to gain approval from the Human Fertilisation and Embryology Authority (HFEA), and later that all hES cell research had to gain approval from the UK Stem Cell Bank, and (ii) permissive in that once permission was granted research deemed illegal in some other countries could be conducted. This 'pro-science' attitude in the United Kingdom (Hauskeller, 2004) found form in a local biological based on 'institutionally accredited' hES cells with a set of instantiated regulatory mechanisms to pursue it.

Japan, in contrast, lacked a legal precedent on embryo research, as In Vitro Fertilisation (IVF) practitioners had been self-regulated under guidelines from the Japan Society of Obstetrics and Gynaecology. The first move on the derivation and use of hES cell lines came when the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) introduced guidelines in 2001:

> Human embryos and ES cells shall be handled carefully and conscientiously without violating human dignity, taking it into consideration that a human embryo is the beginning of a human life and that human ES cells have the potential to differentiate into any type of human cell.
>
> (Ministry of Education, Culture, Sports, Science and Technology (Japan) (MEXT), 2001, Article 3)

This regulatory form in principle sought to support hES research, while responding to the growing concerns about the ethics of human embryo use. In practice, it resulted from a series of political discussions among academic and non-academic intellectuals that corresponded closely with debates taking place in the West, in particular the United States. The debate had no involvement from broader Japanese publics, and as a result little attempt was made to focus the regulatory policy on the ethical and religious specificities of the Japanese population (Kato, 2005; Sleeboom-Faulkner, 2008). In adopting a perspective primarily based on the debates in the West, the MEXT guidelines tightly regulated the derivation and use of hES cells without prohibiting them. Recognizing therapeutic potential of hES cells, the Ministry also ensured compliance with dominant socio-technical discourses emanating from the United Kingdom and United States that tried to strike a balance between getting hES cell research done and protecting human embryos.

Despite this attempted adoption of Western arrangements, many stem cell scientists in Japan felt that in practice the MEXT guidelines were 'irrationally' tight (for example, Nakatsuji, 2007). The guidelines required all research proposals be vetted twice: first by the host institutions' Institutional Review Board (IRB) and second by MEXT itself. This two-tier process generally took over a year to complete, if it was completed at all. Applications often faltered as IRBs acted very cautiously in granting approval. They feared sending projects that they had deemed suitable to MEXT's final review in case MEXT chose to overturn their decision. Failure in the second tier would reflect badly on both the IRB and the broader host institution, particularly as research proposals were evaluated on two specific criteria: (i) their ethical appropriateness, and (ii) the researcher's technical and infrastructural capability. If MEXT rejected a proposal, it implied either the IRB was not capable of making ethically sound decisions or that the host institution lacked the necessary technical and infrastructural capacity. So entrenched were these cautious attitudes that Nakatsuji's laboratory at Kyoto University remained the only group in Japan to establish hES cell lines for almost a decade.

The perceived lack of knowledge about hES cells shaped the precautionary approach of MEXT's 2001 guidelines. They prohibited any "clinical research applying human cells or cells originated from [embryos] to the human body" as well as "utilization of them in medicine and in its related fields" (MEXT, 2001, Article 2 (2)). This made basic research with hES cells difficult and clinical research impossible, and it led many researchers in Japan to avoid hES cells altogether and focus on mouse ES cells or other human cells instead. The Royal Society of Engineering's mission recognized this as a significant problem in 2003, stating they "were surprised to see so much work on embryonic stem cells which, although interesting and rewarding from a scientific point of view, cannot lead to any commercial or clinical advance in the foreseeable future since Japanese regulations do not allow the therapeutic use of [hES] cells" (RAoE, 2003, p. 53).

The unwillingness of the Japanese government to actively support hES cell research remained evident in MEXT's 2003 work program. The 5-year project – the Project for Realization of Regenerative Medicine – was structured around three research areas: the development of stem cell controlling techniques, the development of stem cell therapies and the establishment of a stem cell bank for research purposes. None of these areas, including the stem cell bank, highlighted hES cells explicitly. Instead the emphasis was on other kinds of multipotent stem cells – including mesenchymal and cord blood stem cells – and it further reinforced existing barriers to Japanese hES cell research. Acknowledging the restrictiveness of

their own policies, MEXT advocated that a further revision of the guidelines were required. While the committee to do so formed in December 2003, the revisions did not come into force until early 2007 and once in place still failed to relax any of the conditions in the previous document apart from a small provision allowing organizations beyond Nakatusji's laboratory to distribute its hES cell lines (MEXT, 2007a). This provision in principle made establishment of a research-focused stem cell bank possible. A researcher we interviewed commented that "the committee members were reluctant to make major change" unless they had "concrete evidence" that hES cells work as invaluable clinical tools. While the Japanese approach had targeted a vibrant and successful hES cell research portfolio modeled on the Western approach, the practical instantiation of regulatory measures resulted in an overly restrictive environment and led to stagnation in the field.

The contrast with the United Kingdom is stark. In 2002 *Business Week* presented the United Kingdom as the world leader in stem cell technology with the declaration: "In stem cell research, it's rule Britannia" (cited in Franklin, 2005, p. 59). That year the Select Committee of the House of Lords published a report in stem cell research that argued human "ES cells have significant potential for developing new therapies" (House of Lords Stem Cell Research Select Committee (UK) (HoL), 2002, p. 15). The report acknowledged the ethical discussion over the status of the early embryo and agreed with the findings of the 1980s Warnock Committee on IVF and embryology – that lead to the establishment of the HFEA – that "[f]ourteen days [since fertilization] should remain the limit for research on early embryos" (p. 48), in effect supporting the derivation of hES cells. To promote robust ethical practice in this area, the committee endorsed the "Department of Health's proposals to establish a stem cell bank overseen by a steering committee, responsible for the custody of stem cell lines, ensuring their purity and provenance and monitoring their use" (p. 50). By late 2002 the UK Stem Cell Bank was established.

The House of Lords report also strongly encouraged continued funding for adult stem cell research, which does not involve destroying embryos. While the conventional view in the United Kingdom at the time was that adult stem cells exhibit limited therapeutic value compared with hES cells because they were seen only capable of producing tissue of a related cell type, the report noted 'recent' suggestions about the "[i]ncreased plasticity of adult stem cells" (HoL, 2002, p. 14), reporting some feedback from the UK stem cell community that this potential may make hES cell research "unnecessary" (p. 17). However, "the evidence of the great majority of scientific and medical research organisations […] did not support this view" as "it is unlikely that adult stem cells will fulfil all therapeutic needs" (p. 17). Furthermore, "the full potential of adult stem cell research […] is unlikely to be realised without research on ES cells […] because […] ES cells provide the only realistic means at present of studying the mechanisms and controls of the processes of differentiation […] if safe and reliable therapies are to be developed, a comparison with human ES cells must eventually be made" (p. 17). By making these statements this key governmental body was both legitimizing and endorsing the ethical use of hES cells.

By 2004 the UK Stem Cell Bank had established a state-of-the-art laboratory space to begin receiving cell line deposits (Stacey, 2004; Stephens *et al*, 2008a, b). It was the first bank of its kind in the world and operated with the ethical oversight 'Steering Committee' as recommended in the House of Lords report. The committee is comprised of experts from diverse backgrounds, including bioethicists, clinicians, stem cell scientists, disease group

representatives and sociologists; a range of expertise that committee members described in interview as "most extraordinary", "quite a challenge", "hugely important" and even something to "enjoy" (see also Stephens *et al*, 2008a).

Any laboratory in the United Kingdom with a HFEA license to derive hES cell lines had to deposit them in the Bank. Laboratories in other countries were also permitted to deposit, and several did. This led the Steering Committee to develop mechanisms for judging the provenance and ethical suitability of potential deposits, and the appropriateness of potential applications to access the cells from laboratories in the United Kingdom and abroad interested in conducting research with deposited cell lines. In interview, committee members describe how "with difficulty, the committee had to try to reach a consensus about what was really essential and what wasn't really essential", a process inducing shared judgements about how to recognize appropriate, and less frequently inappropriate, provenance: "I suppose the lesson has been learnt that most of the time, most things are okay". The criteria for 'okay' was formulated in the Steering Committee's (2005) Code of Practice for the use of human stem cell lines that stated hES cell lines must "have been ethically sourced, with fully informed donor consent, and that the cell lines present a valuable resource for the biomedical research community" (p. 11). The importance not only of doing this work, but also of being seen to be doing this work, was clearly understood. As one committee member noted in interview, their committee "is there as a way of reassuring all sorts of different communities that there is a regulatory framework; somebody is responsible for checking that this stuff is not going in directions we don't want it to go in". As Hauskeller (2004) argues, these transparency practices are an important characteristic of the British way of managing difficult issues, like the ethics of human embryos.

The progressive establishment of an ethical source of hES cells in the United Kingdom allowed focus to turn to pursuing this local biological in international stem cell science. The 2005 UK Stem Cell Initiative was established by the then Chancellor – Rt Hon Gordon Brown – to "produce a vision and strategy to keep the UK at the leading edge of global stem cell research over the next decade" (UK Stem Cell Initiative, 2005, p. 40). Their list of 10 strengths of UK stem cell science included a supportive government, favorable ethical environment and world-class researchers, and the UK Stem Cell Bank. While "crucial" the report notes the Bank "is currently synonymous with embryonic stem cell lines" but "should ensure that it develops expertise in … stem cell lines from all sources including adult stem cells" (p. 69). Furthermore, it "should become the international centre in the development of stem cell banking protocols, processes and techniques, such as cryogenics, infection control and Good Manufacturing Practice (GMP)" (p. 69). The same report notes "[t]he Japanese Government stance towards stem cell research is firmly in line with that of the UK" (p. 34) although research "has remained to a large extent held back by the slow development of the regulatory framework" (p. 35). This statement indicates an attempt to enroll Japanese stem cell research into the UK local biological.

By the end of 2005 the Bank had taken deposits of the first hES cell lines derived in the United Kingdom and were prepared to distribute them to any applicant approved by the Steering Committee (UK Stem Cell Bank, 2005). Establishing the Bank had involved challenges and had met some initial concerns within the UK stem cell community around its role and the bureaucratic nature of its procedures (Stephens *et al*, 2011b). However there was a growing sense within the community that the UK Stem Cell Bank was delivering an ethically

robust mechanism for the establishment and distribution of hES cell lines that was emblematic of the UK's international stem cell science portfolio. As the Bank's Director articulated in interview, the United Kingdom saw itself as world leading and was keen for the rest of the world to follow:

> I think the UK model is increasingly being held up as the way to go. In California, in China, in Korea they see that the work that's being done is well grounded in making sure that all the ethical, legal and technical issues have been dealt with before we've actually launched into the work … I think this is something that the UK has really taken a lead in, given other countries' confidence in what they're going to do.

However, an alternative model was emerging, which would also have international impact in the field.

iPS Cells: A New Local Biological in Japan, Resistance within the Established Local Biological of the United Kingdom

In November 2006, Yamanaka's group at Kyoto University published work identifying four genes addable to mouse fibroblasts that suggested pluripotent behavior (Takahashi and Yamanaka, 2006). This induced pluripotency meant the cells could take on a broader differentiation potential beyond the confines of its linage and thus mimic some of the growth potential of hES cells. By late 2007, the international press reported two further groundbreaking publications, one by Yamanaka's group in *Cell* (Takahashi *et al*, 2007) and one by Thompson and Yu at the University of Wisconsin-Madison in *Science* (Yu *et al*, 2007), demonstrating similar successes with human fibroblasts. Using similar but different techniques, both groups claimed to have produced pluripotent stem cells from human adult cells. The media reported these developments as a breakthrough in the science, as much as the ethical guardianship, of stem cells (for example, Cyranoski, 2007; Vogel and Holden, 2007; Wilmut, 2009).

It is not difficult to see why these developments were greeted with such celebration. As Takahashi and Yamanaka (2006) suggest in their first publication, iPS cells gave new life to the therapeutic promises of hES cells, and to the regenerative medicine narrative that had stimulated public imaginations around the world, but now without the need to destroy human embryos. The invention, thus, could be framed as a decisive intervention into the religious and moral controversy on the use of hES cells, which had resulted in complex regulatory structures in some countries, including the UK Stem Cell Bank, and an outright ban of their study in others.

Furthermore, inducing pluripotency in the healthy cells of a diseased patient's own cells could minimize the chance of immunological rejection. A Japanese interviewee described this as "the major advantage of using patient-derived stem cells" over hES cells. The new promise offered was that iPS cells could provide all the functionality of hES cells without any of the ethical drawbacks and possibly with less medical complications. While some researchers remained cautious about these claims, many, including this interviewee, were confident that "further study on the new pluripotent stem cells would soon demonstrate their safety and confirm their clinical usefulness". If the promise held true, it could lead to dramatic reconfigurations of international stem cell policy as well as stem cell science.

The Japanese government was quick to recognize the importance of the iPS cell development, and within a month of Yamanaka's and Thomson and Yu's publications, MEXT published the policy document *iPS Saibou (Jinkou-Tanousei Kansaibou) Kenkyu nado no kasokuni muketa Sougou Senryaku* (The General Strategy to Promote iPS Cell Research). The Ministry was particularly concerned about the need to claim, and also protect, iPS cell research as a 'Japanese' invention, with the competitive challenge from other countries most visibly displayed in the simultaneous publication of successful human iPS cell research by Japanese and American laboratories (Mikami, 2015). Attempting to address this, the General Strategy listed plans to provide extensive support to Yamanaka's group and others working on iPS cells in the country. Among the plans were (i) the establishment of the Working Group of Strategy for Stem Cells and Regenerative Medicine, (ii) the establishment of a central research institution of iPS cells at Kyoto University and (iii) the development of a consortium for iPS cell research (MEXT, 2007b). All of these plans were implemented within a couple of months after the publication of the General Strategy, and Yamanaka became the central figure in all three organizations – the Working Group, the Center for iPS cell Research and Application (CiRA) and the iPS Network – indicating his rapidly increased importance in Japanese stem cell research. Further financial support shifted toward iPS cell research, with MEXT's Project for Realization of Regenerative Medicine, the Council of Science and Technology Policy, and two other government ministries backing these efforts. The response was positive, with one interviewee declaring "the government support definitely improved the research environment for stem cell scientists". This more positive attitude, and the policy changes allied to it, contributed to the emergence of a new Japanese biological based on 'technically advanced' pluripotent stem cells. While some resentment remained among scientists working in other areas, stem cell science in Japan shifted into this new local biological and diverted away from the 'cell bank' model being diffused globally from the United Kingdom.

While the announcement of human iPS cells received tremendous attention from scientific and political communities internationally, some clear resistance to this new biological existed. Some were critical of the low success rate of reprogramming; some were concerned about the risk of using a gene called c-Myc as one of the transcription factors in reprogramming because it is known as a cause of tumor formation; and others questioned whether the new cells can be considered exact equivalent to hES cells (Holden and Vogel, 2008). Some of these technical issues were responded to by new research findings: for example, Yamanaka's group refined the technique to produce iPS cells without the Myc-gene family (Nakagawa *et al*, 2008). However, such technical advance also posed new questions about the technique. While various new ways of inducing pluripotency to adult cells were being developed, some were very different to the initial method (Okita *et al*, 2008; Stadtfeld *et al*, 2008; Zhou *et al*, 2009). This raised questions about which approach is the best, in terms of both safety and efficiency for clinical use. Furthermore, others argued reprogramming does not need to induce pluripotency but remains useful if it only turns adult cells into one different lineage (Ieda *et al,* 2010). Equally a new ethical focus emerged associated with iPS cells, which was different to those framing hES cell debates: Zarzeczny *et al* (2009) articulate how new and existing issues, including consent, reach-through rights, intellectual property, clinical translation and ethical usage, could be relevant in this case. Quigley *et al* (2012) further complicate the issues in considering the ramification of making germ cells through iPS cell techniques and the potential of producing viable embryos, as has been achieved in mice.

Responding to such initial reactions, the Japanese government adopted a strategy to promote iPS cell research even further, and went so far as to relax existing guidelines that had previously inhibited hES cell research. The rational for this relaxation was based on the expected benefit for iPS cell research of allowing comparative hES cell work, because, as one interviewee put it, "iPS cell and hES cell research are the wheels on a single axle". In 2009, MEXT revised its guidelines on hES cell research again, dividing them into two distinctive sets of regulations: the Guidelines on the Derivation and Distribution of Human Embryonic Stem Cells (MEXT, 2009a) and the Guidelines on the Utilization of Human Embryonic Stem Cells (MEXT, 2009b). Under these new guidelines, researchers in Japan are in principle able to conduct research on established hES cell lines by receiving the approval only from the IRB, rather than going through the two-tier system. The guidelines were further revised in 2010, when the creation of germ cells from both hES cells and iPS cells became permitted (MEXT, 2010a, b). The move toward ethically contentious territory of this particular revision surprised many, including one of our interviewees who described the creation of germ cells as "only a step away from creating embryos". Together these changes demonstrate a dramatic shift in the mode of governance in this field: in the pre-iPS years, Japan had not been able to make a major change in its regulatory arrangements and it took 6 years to produce one small revision of the guidelines; post iPS, in contrast, Japan acted swiftly and introduced a number of rapid and radical regulatory revisions – all directed toward the advance of iPS cell research – within a short period of time. Furthermore, in the interests of developing the Japanese iPS cell research portfolio, procedures with hES cells that were previously prohibited were sanctioned overturning years of restrictive regulation. This new local biological was taking hold.

The importance of the first publications on iPS cells was also recognized within the UK regulatory system. Our ethnographic fieldnotes detail the first meeting of the UK Stem Cell Bank Steering Committee – the Bank's guidance and ethics oversight group – following the announcement at which the potential impacts of iPS cells were discussed. In a highly speculative discussion the interdisciplinary group considered what the technology could mean for them and the Bank. The question was raised that if the Steering Committee's primary role is providing rigorous ethical guardianship for a sensitive biological material – hES cells – and that the functionality of this material could now potentially be replaced by a non-controversial substitute – iPS cells – then what need would there be for the Steering Committee in the future? A range of views were expressed, but the idea was entertained that if iPS cells really did deliver the functionality of hES cells and really did prove to be no more ethically sensitive than existing adult stem cell procedures, then indeed the importance of the Steering Committee, and by implication that of the UK Stem Cell Bank, might be significantly reduced. This was couched in a number of questions over whether the claims concerning the value of iPS cells were really reliable, and an acknowledgment that the Steering Committee remained responsible for those hES cell lines already in circulation.

Through this context the UK Stem Cell Bank continued to work on developing best practice in the technical and ethical guardianship of hES cell lines in global stem cell science. Perhaps most noticeably, this occurred through their directorship of the International Stem Cell Banking Initiative (ISCBI) from 2007 onwards. This project brought together representatives from 17 countries, including Japan. As the UK Stem Cell Bank's Director describes: "I contacted the groups that I knew were actually banking cells, and who I felt were important to be there to have a balanced meeting… the people aware of the shipping issues, the quality

control issues, the technical difficulty of the actual work that's being done, be aware of ethical and other regulatory guidelines in their own country, so that we can get together and consider the best practice for the banking, documentation, distribution, quality control and dealing with ethical differences between different countries". The consortium worked to share procedures and encourage the establishment of new banks in countries where such an institution did not exist (Crook *et al*, 2010). The first output from the project was delivering consensus guidance for banking and supply of hES cells that was also argued to be applicable to iPS cells (International Stem Cell Banking Initiative, 2010).

The progressive appearance of the Japanese local biological in the United Kingdom can be observed in the 2010 version of the Steering Committee's code of practice for the use of human stem cell lines, noting that iPS cells "are believed to be like embryonic stem cells in many respects" (Steering Committee for the UK Stem Cell Bank and For the Use of Stem Cell Lines, 2010, p. 8) although "[t]he full extent of iPS cells' relationship to natural pluripotent stem cells such as embryonic stem cells is still being assessed" (p. 8). It makes clear that while the deposit of UK-derived hES cells is mandatory "[t]here is no such requirement to deposit iPS cells, fetal or somatic stem cell lines within the UK Stem Cell Bank, although the Steering Committee will consider applications to bank such lines where these are likely to provide a valuable resource for research" (p. 9). iPS cell research is now common in the United Kingdom and the regulatory position is equivalent to other adult stem cell research; meaning that there is no specific role for the UK Stem Cell Bank or the HFEA to oversee its governance, unless reproductive cells are being produced in which case the HFEA are again implicated.

While iPS cell research flourishes along with hES cell research in the United Kingdom, it can be argued that, although to a lesser extent, the claim of the 2005 UK Stem Cell Initiative that the UK Stem Cell Bank is "synonymous with embryonic stem cell lines" still holds. In early 2012, the Bank held 61 UK and 27 foreign-derived hES cell lines compared with one fetal and no iPS cell lines. In practice, a great many UK researchers conduct iPS cell research, but the UK local biological remains more closely tied to the hES cell trajectory. Similarly, the emergence of the new Japanese biological was not an overnight event, and the influence of the UK Stem Cell Bank remained observable in Japan. In 2009, the Japanese representative of the ISCBI in interview emphasized the importance of being part of such an initiative – noting "no one wants to stand alone" – and suggesting that hES cells might be safer than iPS cells for clinical use. However, this type of opinion became progressively marginal following the large government support for iPS cell research that allowed extensive study of its safety and efficacy and increasingly convinced researchers in Japan that iPS cells are both ethical and clinically useful. The same period saw little progress in hES cell research.

Contesting Local Biologicals: The Politics of Standardization in Stem Cell Science

The story in this article so far has been one of initial similarity between the Japanese and United Kingdom approaches to hES cell research and subsequent divergence. When the mission of the Royal Society of Engineering visited Japan in 2003, the two countries were pursuing strategies to establish themselves as world leaders in stem cell science, both articulating a local biological around the promise of high-tech biology that could have its

ethical challenges controlled by robust regulatory mechanisms, leading to national financial reward, health gains and prestige (cf. Hauskeller, 2004). However, the initial responses from the two governments were slightly different: while they both allowed hES cell research in principle, particularly by introducing transparency in its governance, the Japanese regulation proved unanticipatedly discouraging. As time passed, the difference became even clearer as the United Kingdom put into place institutions and mechanisms to materialize this vision: the UK Stem Cell Bank was established in 2003 promoting the ethical use of hES cells in the United Kingdom and overseas. It actively engaged in international collaborations through its directorship of the ISCBI, one part of a broader socio-technical arrangement that worked to instantiate a vision of 'institutionally accredited stem cells'. In contrast, regulatory complication remained in Japan for approximately 6 years, and, during this period, many Japanese researchers avoided hES cell research. The emergence of human iPS cells in 2007 triggered the beginning of a strategic divergence as Japan entered a period of rapid regulatory change as afforded by a new iPS cell orientated vision, essentially opting for the 'technically advanced stem cells' in response to the ethical and regulatory challenge of hES cells by pursuing this embryo-free alternative.

Set within this context is a new politics of standardization, pitting hES cells and the UK approach against iPS cells and the Japanese approach. Hauskeller and Weber (2011) have already documented the complex relationship between hES and iPS cell technologies with their ethnographic studies in the United Kingdom and Germany. In their study of laboratory researchers, they describe how:

> [for the laboratory researchers studied] the significance of iPS cells is constructed around the fact that their potential is the *same* as hES cells as regards their pluripotency. Yet, in arguing that research on iPS and hES cells must evolve in parallel, they are also framed as *different* in that little is known about their status *vis-à-vis* hES cells. Implicitly, hES cells are presented as having a stable status as scientific objects against which the properties of iPS cells can be measured and determined.
>
> (Hauskeller and Weber, 2011, p. 422, emphasis in original)

This is a common framing of the issues as found in both Germany and the United Kingdom, indicating what Hauskeller and Weber (2011, p. 427) call "global discursive repertoires" formed through international exchange of bioethical discourses and technical knowledge. Networks including the International Stem Cell Initiative and stem cell banks such as that in the United Kingdom are identified as key actors in facilitating this exchange. We identify similar constructions about the relationships between hES and iPS cells within our regulatory settings.

Our comparison, however, questions what form such discursive repertoires take as well as to what extent they really are global. The framing identified in the United Kingdom and Germany comparison suggests that iPS cell researchers bear the burden of proving their equivalence to hES cells. Behind this burden is the assumption that iPS cells are artificial mimicry of natural hES cells, as also observed by Hauskeller and Weber:

> These accounts convey three important notions that characterise hES cells in relations to iPS cells: (a) hES cells are portrayed as established objects of research practice, especially suited as models for experimental control; (b) hES cells become

> the "normal" pluripotent stem cells. This normalisation takes place within the linear model of development that takes the hES cell as representing an early stage of differentiation from which all latter cell types derive and which is defined by "natural" pluripotency; (c) the pluripotency of iPS cells as the product of genetic intervention in the laboratory is implicitly presented as not natural, an artificially produced property. This pluripotency of iPS cells needs to be checked against the "normal" pluripotency of hES cells.
>
> (Hauskeller and Weber, 2011, p. 423)

This is also explicit within the UK Stem Cell Bank's Steering Committee's 2010 version of the code of practice for the use of human stem cell lines in the United Kingdom: "[t]he full extent of iPS cells' relationship to *natural* pluripotent stem cells such as embryonic stem cells is still being assessed" (Steering Committee for the UK Stem Cell Bank and For the Use of Stem Cell Lines, 2010, p. 8, emphasis added). By defining iPS cells in relation to hES cells the United Kingdom approach renders the Japanese biological as an underdefined contestant to their 'institutionally accredited' pluripotent stem cells.

Importantly, the construction of hES cells as natural assumes a particular set of meanings and constellation of socio-technical resources in its accomplishment. Embedded within this is the notion that hES cells are natural because, unlike iPS cells, they do not require genetic modification techniques. However, outside of laboratory settings hES cells only exist during a transitional state early in embryo development before they differentiate into cells with less differentiation potential in the course of its 'natural' development after fertilization. In the laboratory context, the cells are removed from embryos and artificially immortalized. As Landecker observed for HeLa cells, the cells are "freed from the bounds of the body" and simultaneously "from the limits of the originating organism's life span" (2007, p. 11). Therefore, despite the common assumption about their naturalness, hES cells can also be understood as unnatural. The higher chance of immunological rejection after transplantation further supports this understanding of their unnaturalness, at least, if inserted in a patient's body (cf. Lock, 2002). The assertion of 'naturalness', and any subsequent comparative criterion premised upon it, is a key component of the politics of standardization in global stem cell science.

There has been a struggle to standardize hES cells since they were first derived. Apart from their provenance in human embryos, the only feature that defines hES cells may be their pluripotency: the ability to differentiate into many cell lineages (Webster and Eriksson, 2008). However, there is no marker or set of markers uniquely expressed in hES cells that defines their pluripotency, and they can only be tested by seeing if they form teratomas in animal models. If a standard marker did exist, as Eriksson and Webster (2008) point out, it would serve as a performative standard establishing the potentiality of hES cells to be other cells in the future without relying upon animal teratoma tests. Such a standard would be important in our context because the same marker could then be used to test if pluripotency of iPS cells is underpinned by the same biological mechanisms as that of hES cells, and thus the 'articifial' stem cells can be tested if they are equivalent to the 'natural' stem cells. Currently this remains impossible as different researchers use varying techniques to derive hES cells and deploy different markers to test their state, just as they do to produce iPS cells and to test their state. An international attempt to address this gap

and reach agreement on markers for hES cells, led by the International Society for Stem Cell Research, failed to identify an agreed standard.

In this context, the activities of the UK Stem Cell Bank become important. While scientists may not be able to agree on performative standards, they seem to be more willing to agree procedural standards. By curating a large number of hES cell lines and improving their culturing techniques, the UK Stem Cell Bank is in a strong position to minimize the gap between different procedures adopted in various locals. It also provides technical support to the recipients of hES cell lines and, by so doing, disseminates its techniques. Furthermore, the assessment at the Bank to accept established cell lines and to distribute them internationally based on ethical and technical criteria reinforces their particular set of standards for the conduct and nature of hES cell research globally. Any international laboratory that wants to deposit or access a cell line with the UK Stem Cell Bank must demonstrate to its Steering Committee that it complies with their standards. Furthermore, the acceptance of a hES cell line at the UK Stem Cell Bank can be ascribed as a guarantor of ethical legitimacy in other jurisdictions, as is the case with funding from the California Institute of Regenerative Medicine (see Hammond-Browning and Stephens, 2013). This spreading of the UK biological is further increased through the UK Stem Cell Bank's directorship of the ISCBI that addresses both technical and ethical best practice. Together with the less-standardized domain of performative standards, the UK Stem Cell Bank has been aiming to produce a standardized package of hES cell research, which would introduce institutional alignments across different local contexts and lead to increased do-ability of hES cell research internationally (Fujimura, 1987).

If successful these processes of standardization would be powerful social devices and, as Star (1991) observes, non-compliance with the standards leads to marginalization incurring extra social burdens for the marginalized. By treating hES cells as the standard type of pluripotent cells, the burden of proof is imposed upon iPS cell researchers. Furthermore, a standardized hES cell could also serve as a boundary object, able to cross between local contexts without losing its significance (Star and Griesemer, 1989). Such high mobility would be an important aspect of any global biological, applying equally to the stem cell case. As Eriksson and Webster (2008) argue, standards in stem cell science "function as stabilizing and enabling tools, and standardization is a common and often successfully applied strategy in new and emerging fields of research, and indeed, acts to recruit and coordinate participants in the field" (p. 64). The discourse of recognizing hES cells as the standard of pluripotency is so powerful that even the Japanese biological has not been able to dismiss it in instantiating its vision of 'technically advanced' stem cells, as witnessed in their relaxation of hES cell guidance in the post-iPS era.

In the same way, the discussion about the clinical potential of iPS cells cannot be ignored in instantiating the vision of 'institutionally accredited' stem cells in the United Kingdom, as evidenced in the reaction from the UK Stem Cell Bank. Even if hES cells were to become more technically stabilized and ethically assured, there remain other ways the clinical advantage of iPS cells over hES cells could be established. One possible example is the potential therapeutic use of patients' own iPS cells mitigating immunological-compatibility issues, widely known as autologous cell therapy (Takahashi and Yamanaka, 2006). That noted, in Japan, MEXT has been moving away from this autologous cell therapy model, considering it too expensive and time-consuming. Instead, Japanese researchers now work to establish a hospital-based iPS cell bank to distribute clinically useful non-patient specific iPS cell lines for therapeutic use

(Cyranoski, 2012). While the iPS cell bank currently lacks the transparency in governance and the breadth of functionality seen at the UK Stem Cell Bank, we suggest it may still develop to become recognized as a stable site for sourcing safe and efficient cell lines, should further research demonstrate the clinical usefulness of iPS cells. This could furnish the iPS cell field with a set of *de facto* standards (see Sengoku *et al*, 2011) or design standards (Eriksson and Webster, 2008) that become dominant through serving a majority without attaining formal agreement from all within a community. If achieved, the impact of this on the UK Stem Cell Bank could be significant. In the short term, the threshold that individual applications to the UK Stem Cell Bank would need to meet in terms of establishing that their proposed hES cell research could not be accomplished through other means would be raised, with applicants needing to prove an iPS cell project is not a viable alternative (Hammond-Browning and Stephens, 2013). In the longer term, questions could be raised about the very necessity of the ethical guardianship role played by UK Stem Cell Bank, beyond overseeing those hES cell lines already in circulation.

These moments – the work on technical standardization in the United Kingdom and the establishment of an iPS cell bank in Japan – are significant moments because they mark a curvature in the post-2007 trajectories in the two countries. While the period immediately following the emergence of human iPS cells saw both the United Kingdom and Japan journeying on different and distinctive paths, we subsequently see both countries coming full circle to challenge and inform each other. For the UK socio-technical arrangements to globalize, they must move beyond their institutional accomplishments to grapple with the technical feats of establishing a standardized set of markers that validate the pluripotency of hES cells. If this were achieved, the increased do-ability of hES cell research across different contexts could undermine the Japanese local biological and limit the significance of iPS cell invention. In this case, hES cells could globalize as the UK biological becomes internationally accepted and totalizes the field of stem cell science. Alternatively, for the Japanese socio-technical arrangements to globalize, they must attain a level of institutional stability to assert the clinical usefulness of iPS cell therapies in the medical system. If this were achieved, iPS cells could be presented as having a stable status as *clinical* objects, in contrast to Hauskeller and Weber's (2011) account of hES cells as scientific objects (see also Wainwright *et al*, 2009 for related discussion). The institutionalized guardianship of hES cell ethics, represented by the work of the UK Stem Cell Bank, could be deemed unimportant, or even unnecessary. In this case, iPS cells could globalize as the Japanese biological becomes diffused and dominating in this international field.

Conclusion

Stem cell science exhibits ongoing expansion. The establishment of the first hES cell line in 1998 served as the trigger, and the potential of stem cells for therapeutic use, which is largely underpinned by the pluripotent character of hES cells, is no doubt one major reason for it. However, more importantly, the expansion would not have been possible if stem cell science did not attract political and economic interests on a global scale, that is, in Franklin's (2005) term, the emergence of the global biological enterprise. The strong political commitments from national governments simultaneously created the divergence of

local socio-technical arrangements for stem cell sciences and reinforced the aspect of stem cells as local biologicals.

In seeing scientific, medical and economic potential of hES cell research, the UK government adjusted the regulatory framework established during the debate on IVF and decided to instantiate its vision of 'institutionally accredited' pluripotent stem cells. This vision was further substantiated by several policy reports and the UK Stem Cell Bank established in 2003 was a key component in its pursuit of bringing this locally emerged vision onto the global stage. The Bank soon became recognized as the archetype of hES cell governance and its members contributed to developing internationally standardized protocols for handling hES cells. Thus, the UK local biological was successful in not only legitimizing hES cell science in its local context but also building the United Kingdom's reputation internationally and convincing other countries to follow its approach. The first challenge to this model came with the creation of human iPS cells in 2007. Japan, which failed to create a successful local biological based on a similar vision of 'institutionally accredited' hES cells, rapidly made its decision to commit to the new reprogramming technique and created a new vision based on iPS cells. In contrast to the UK approach, this Japanese vision can be understood as the technical response to the ethical challenge of hES cells shared in global stem cell science, summarized as 'technically advanced' pluripotent stem cells. Today, these two local visions engage in the politics of standardization, undermining the significance of the other to present its global value.

This politics allows us to recognize a local biological as an assemblage inevitably informed by various national socio-technical arrangements: some parts of arrangements developed in one national context transgress national boundaries becoming reframed in another. In this regard we take a step further than Franklin and her account of the local/global biological, by asserting the ways in which the local biologicals of Japan and the United Kingdom are connected, in this instance progressively through processes of standardization and the question about 'naturalness'. In the United Kingdom, efforts to shape international standardization initiatives for hES cells seeks to assert this cell type as the gold standard, in part premised upon a particular construction of the 'naturalness' of hES cell lines. If successful, this would raise the barrier for establishing iPS cells as appropriate candidates to replace them. In contrast, researchers in Japan are now trying to demonstrate the clinical usefulness of iPS cells and establish a cell bank as a stable source of these. If successful, this would question the absolute necessity of hES cell research and hence the importance of the UK Stem Cell Bank as their ethical guardian.

Here, we also see the incompleteness of the two local biologicals evident in the United Kingdom and Japan. On the one hand, the UK local biological was premised upon institutional aspects of hES cell governance invoking the naturalness of hES cells, but now technical development is required to establish the cells as a gold standard. The Japanese local biological, on the other hand, was built upon the technical advancement in stem cell science, namely the reprogramming technique for iPS cells, but a form of institutional stability ensuring its safety as well as its cost effectiveness in medicine is now critical to confirm iPS cells' clinical usefulness. Therefore, we suggest that, while the two countries headed off in distinctive directions in the mid-2000s, they are now incentivized to progress in directions that they had not pursued then, namely creating an equivalent to the socio-technical arrangements instantiated in the other.

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